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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/800,103
Filing Date	03/06/01
First Named Inventor	Donoho
Group Art Unit	1647
Examiner Name	R. S. Landsman
Total Number of Pages in This Submission: 18	Attorney Docket Number: LEX-0143-USA

ENCLOSURES *(check all that apply)*

☐ Fee Transmittal Form	☐ Assignment Papers *(for an Application)*	☐ After Allowance Communication to Group
☐ Fee Attached	☐ Drawing(s)	☐ Appeal Communication to Board of Appeals and Interferences
☐ Amendment / Reply	☐ Licensing-related Papers	☒ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
☐ After Final	☐ Petition	☐ Proprietary Information
☐ Affidavits/declaration(s)	☐ Petition to Convert to a Provisional Application	☐ Status Letter
☐ Extension of Time Request (Original & Copy)	☐ Power of Attorney, Revocation Change of Correspondence Address	☐ Other Enclosure(s) *(please identify below):*
☐ Express Abandonment Request	☐ Terminal Disclaimer	- Return postcard
☐ Information Disclosure Statement	☐ Request for Refund	
☐ Certified Copy of Priority Document(s)	☐ CD, Number of CD(s) _____	
☐ Response to Missing Parts/ Incomplete Application	Remarks	**FILED IN TRIPLICATE**
☐ Response to Missing Parts under 37 CFR 1.52 or 1.53		**Customer # 24231**

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Lexicon Genetics Incorporated Lance K. Ishimoto Reg. No. 41,866
Signature	Lance K. Ishimoto by Robert G Sabatini 41862
Date	February 3, 2004

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express mail label EV322477387US addressed to: Commissioner for Patents, MS Appeal Brief - Patents, P.O. Box 1450, Alexandria, VA 22313 on: February 3, 2004

Typed or printed name	Nancy Stacey		
Signature	Nancy Stacey	Date	February 3, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Donoho *et al.*	Group Art Unit: 1647
Application No.:	09/800,103	Examiner: R. Landsman
Filed:	March 6, 2001	
Title:	Polynucleotides and Polypeptides encoding Human Transporter Proteins	Atty. Docket No. LEX-0143-USA

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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A. Do Claims 1-3 and 13-14 Lack a Patentable Utility?

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apply to a transporter protein. In the Examiner's Answer (page 3, lines 24-26) the Examiner also points to Appellants use of the abbreviation NHP for novel human protein as an indication that Appellants had no idea of the function of the present invention. This is not the case, the abbreviation NHP was simply used for efficiency and to shorten the application. The Examiner also repeatedly points to the multiple descriptions that appear within the specification such as "sugar and sodium-dependent inorganic phosphate transporters, and NBMPR-sensitive nucleoside transporters" as further indications that Appellants had no idea of the function of the present invention at the time the application was filed. However, Appellants note that as determined by the Examiner in the Restriction and Election requirement dated May 30, 2002 (Paper No. 9) that the application as filed described multiple distinct inventions (transporters) and this, not ignorance, lead to the use of multiple identifiers. Furthermore, sugar and sodium-dependent inorganic phosphate transporters are both recognized members of the major facilitator superfamily (MFS) of membrane transporters, also called the uniporter-symporter-antiporter family. MFS transporters are integral membrane single-polypeptide carriers capable only of transporting small solutes in response to chemiosmotic ion gradients and include drug efflux pumps. Thus, such transporter proteins export chemotherapeutics and play a role in multiple drug resistance of human tumors.

The Examiner's Answer also reiterates the Examiner's previously stated position that (page 4, lines 23-25) that "Sequence homology alone cannot be accepted in the absence of supporting evidence, because the relevant literature acknowledges that function cannot be based solely on structural similarity to a protein found in the sequence databases." The Examiners Answer goes on to present a series of articles that have been both previously presented and rebutted by the Appellant. None of these articles constitute evidence that Appellants assertion that the sequences of the present invention encode a novel human transporter protein is not credible. This is because, in addition to the specific issues described with each reference as follows, is the fact that none of the cited articles.

The Examiner's Answer first cites an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall

amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Applicants assertions.

The Examiner's Answer next cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

The Examiner's Answer next cites Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support

that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that transporters represent a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Examiner's position against utility, Doerks *et al.* supports Applicants' position that the presently claimed sequences have a recognized substantial and credible utility.

The Examiner also cites Smith, *et al.* (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 5). However, the Smith, *et al.* article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cites Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Examiner's Answer cites Bork *et al.* (Trends in Genetics *12*:425-427, 1996) as

supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 8 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure - function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork et al. do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Applicants assertions regarding the utility of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more

careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists). Furthermore, there are hundreds, if not thousands of scientific publications indicating that those of skill in the art readily accept that there is clearly a relationship between structure and function and therefore, such an assumption is credible.

In response to the Examiners position in the Examiners answer which suggests that Appellants have not asserted that the sequences of the present invention encode a transporter protein, Appellants reiterate that the specification as filed clearly identifies the sequences of the present invention as encoding a transporter protein. This is clear from the title of the application as filed "NOVEL HUMAN TRANSPORTER PROTEINS AND POLYNUCLEOTIDES ENCODING THE SAME" and as described throughout the specification (for example, page 1, line 12; page 2, line 7, 9-13). In addition the application identifies transporter proteins as integral membrane proteins that mediate or facilitate the passage of materials across the lipid bilayer and identifies the role of transporter proteins in the export of chemotherapeutics and thus their role in multiple drug resistance (specification on page 1, lines 23-31 and on page 3, lines 19-23). The tissue specific expression pattern of this MFS transporter is also described in the specification as filed on page 3, line 30. Thus, clearly Appellants have asserted that the sequences of the present invention encode a novel human transporter protein and as described in the specification as filed (on page 16, lines 19-23) was the role of such transporters and transporter related multidrug resistance (MDR) sequences, as well as uses and applications that are germane to the described transporter as described in U.S. Patents Nos. 5,198,344 and 5,866,699 which were incorporated by reference in their entirety. Furthermore, it even appears that the Examiner eventually does recognize this (on page 6, lines 6-8 of the Examiner's Answer) That "Though Appellants have clearly stated that the protein of the present invention is a transporter protein .....Appellants have still not provided any conclusive evidence that the protein of the present invention is a transport protein."

Additional evidence was previously provided to the Examiner, that further demonstrates that those of skill in the art would find the assertion that the sequences of the present invention encode a transporter

protein credible, was a compilation of the results of functional protein domain analyses using several of the available methods known to and accepted by those of skill in the art as Exhibit A of the Appeal Brief. InterPro (http://www.ebi.ac.uk/interpro/) is a publically database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences. InterPro analysis of SEQ ID NO:2 of the present invention clearly shows it to be, as Appellants have asserted, *a transporter protein.* Pfam (http://www.sanger.ac.uk/Software/Pfam/index.shtml) is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains and families. Pfam analysis of SEQ ID NO:2 of the present invention once again clearly shows the present invention to be, as Appellants have asserted, *a transporter protein.* ProtComp analysis (http://www.hgmp.mrc.ac.uk/GenomeWeb/prot-anal.html)is used in identifying sub-cellular location of a protein in animals and fungi. Results of a ProtComp analysis of SEQ ID NO:2 of the present invention shows it to be an integral membrane protein. Appellants have asserted that the sequences of the present invention encode a transporter protein, whose function is to mediate or facilitate the passage of materials across the lipid bilayer, thus logically those of skill in the art would recognize that *transporter proteins are very often integral membrane proteins.* SMART (a Simple Modular Architecture Research Tool: http://smart.embl-heidelberg.de/) analysis allows the identification and annotation of genetically mobile domains and the analysis of domain architectures. More than 500 domain families found in signaling, extracellular and chromatin-associated proteins are detectable. These domains are extensively annotated with respect to phyletic distributions, functional class, tertiary structures and functionally important residues. Each domain found in a non-redundant protein database as well as search parameters and taxonomic information are stored in a relational database system. SMART analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, a *transporter protein.* TMHMM analysis (http://www.cbs.dtu.dk/services/TMHMM/) predicts transmembrane helices in proteins and TMHMM analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be an integral transmembrane protein, as those of skill in the art would expect of a *transporter protein.* Finally, ProDom analysis (http://prodes.toulouse.inra.fr/prodom/2002.1/html/home.php) is a comprehensive set of protein domain families automatically generated from the SWISS-PROT and TrEMBL sequence databases.

ProDom analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, *a transporter protein*. In summary, all of the evidence presented as a result of analysis using a series of different methods recognized by those of skill in the art, clearly agree and identify the sequences of the present invention as encoding an integral membrane transporter protein, as Appellants had asserted in the specification as filed. Therefore, clearly, Appellants' assertion that the sequences of the present invention encode a transporter protein are credible and would be accepted by those of skill in the art.

Finally, the Examiner appears to recognize that transporter proteins have specific and substantial utility (lines 10-12 on page 6 of the Examiner's Answer) and Appellants submit that the legal test for utility is not "conclusive evidence", rather simply an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Therefore, as Appellants have made the credible assertion that the sequences of the present invention encode a MFS transporter protein and transporter proteins are known to have specific and substantial utility and play a role in multiple drug resistance by human tumors, the logical conclusion is that the sequences of present invention also have patentable utility and rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

The Examiner also discounts several arguments concerning the utilities of the sequences of the present invention since other nucleic acid sequences can be used in a similar fashion. In addition to the detailed arguments presented by Appellants in the Appeal Brief with regard to each of these asserted utilities, Appellants once again point out that these arguments are completely rebuffed by the Federal Circuit's holding in *Carl Zeiss, supra* ("[A]n invention need not be the best or only way to accomplish a

certain result"). As the main argument concerning this utility and that of use of the specific sequences on DNA chips (presented below) is that since other nucleic acid sequences can be used to map the human chromosome or on DNA chips, these do not represent specific or substantial utilities. However, as previously presented, don't all golf balls and tires have the same utility of other golf balls or tires, i.e. they can be used as golf balls or tires respectively and yet these items are readily considered to have patentable utility.

Furthermore, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. In fact some such gene chips have contained randomly generated sequence.

However, in contrast the sequences of the present invention provide a specific marker of the gene that is transcribed, spliced and encodes a novel human transporter that is expressed in some human tissues and not others. Thus, these sequences provide a unique identifier of the corresponding gene in the human genome. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the

specification details. The Examiner agrees that such "DNA chips" have utility, as evidenced by hundreds of issued U.S. Patents, but argues that specific sequences which clearly increase the utility of a patented invention do not. It must be noted that this position runs counter to that made by the Examiner regarding golf balls, wherein the presence of a specific feature that enhances the utility of the golf ball has utility.

For each of the foregoing reasons, as well as the reasons set forth in the Appeal Brief, Appellants submit that the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 1-3, 13 and 14 Unusable Due to a Lack of Patentable Utility?

Regarding the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility, Appellants submit that as claims 1-3, 13 and 14 have been shown to have "a specific, substantial, and credible utility", as detailed in Section X(A) above, as well as Section VIII(A) of the Appeal Brief, the present rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, must be overruled.

XI. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-3, 13 and 14 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

February 3, 2004
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appellants do not wish to restate all of the arguments presented in the Appeal Brief concerning the Examiner's allegation that claims 1-3 and 13-14 lack a patentable utility, and instead incorporate the entirety of Section VIII(A) of the Appeal Brief at this point herein by reference. However, Appellants feel the need to specifically address several of the arguments presented in the Examiner's Answer in some detail for the record.

The Examiner is attempting to reject the present application based on the position that no assertion of specific and substantial utility for the claimed invention has been made. Appellants respectfully strongly disagree. In support of this position, the Examiner states in the Examiner's Answer (page 3, lines 23-24) that "It is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art." This is incorrect as the Appellants have asserted that the sequences of the present invention encode a novel human transporter protein, not a receptor and the term "orphan receptor" indicates a receptor whose ligand has yet to be identified. The phrase "orphan receptor" does not correctly

apply to a transporter protein. In the Examiner's Answer (page 3, lines 24-26) the Examiner also points to Appellants use of the abbreviation NHP for novel human protein as an indication that Appellants had no idea of the function of the present invention. This is not the case, the abbreviation NHP was simply used for efficiency and to shorten the application. The Examiner also repeatedly points to the multiple descriptions that appear within the specification such as "sugar and sodium-dependent inorganic phosphate transporters, and NBMPR-sensitive nucleoside transporters" as further indications that Appellants had no idea of the function of the present invention at the time the application was filed. However, Appellants note that as determined by the Examiner in the Restriction and Election requirement dated May 30, 2002 (Paper No. 9) that the application as filed described multiple distinct inventions (transporters) and this, not ignorance, lead to the use of multiple identifiers. Furthermore, sugar and sodium-dependent inorganic phosphate transporters are both recognized members of the major facilitator superfamily (MFS) of membrane transporters, also called the uniporter-symporter-antiporter family. MFS transporters are integral membrane single-polypeptide carriers capable only of transporting small solutes in response to chemiosmotic ion gradients and include drug efflux pumps. Thus, such transporter proteins export chemotherapeutics and play a role in multiple drug resistance of human tumors.

The Examiner's Answer also reiterates the Examiner's previously stated position that (page 4, lines 23-25) that "Sequence homology alone cannot be accepted in the absence of supporting evidence, because the relevant literature acknowledges that function cannot be based solely on structural similarity to a protein found in the sequence databases." The Examiners Answer goes on to present a series of articles that have been both previously presented and rebutted by the Appellant. None of these articles constitute evidence that Appellants assertion that the sequences of the present invention encode a novel human transporter protein is not credible. This is because, in addition to the specific issues described with each reference as follows, is the fact that none of the cited articles.

The Examiner's Answer first cites an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall

amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Applicants assertions.

The Examiner's Answer next cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

The Examiner's Answer next cites Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support

that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that transporters represent a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Examiner's position against utility, Doerks *et al.* supports Applicants' position that the presently claimed sequences have a recognized substantial and credible utility.

The Examiner also cites Smith, *et al.* (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 5). However, the Smith, *et al.* article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cites Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Examiner's Answer cites Bork *et al.* (Trends in Genetics *12*:425-427, 1996) as

supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 8 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure - function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork et al. do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Applicants assertions regarding the utility of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more

careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists). Furthermore, there are hundreds, if not thousands of scientific publications indicating that those of skill in the art readily accept that there is clearly a relationship between structure and function and therefore, such an assumption is credible.

In response to the Examiners position in the Examiners answer which suggests that Appellants have not asserted that the sequences of the present invention encode a transporter protein, Appellants reiterate that the specification as filed clearly identifies the sequences of the present invention as encoding a transporter protein. This is clear from the title of the application as filed "NOVEL HUMAN TRANSPORTER PROTEINS AND POLYNUCLEOTIDES ENCODING THE SAME" and as described throughout the specification (for example, page 1, line 12; page 2, line 7, 9-13). In addition the application identifies transporter proteins as integral membrane proteins that mediate or facilitate the passage of materials across the lipid bilayer and identifies the role of transporter proteins in the export of chemotherapeutics and thus their role in multiple drug resistance (specification on page 1, lines 23-31 and on page 3, lines 19-23). The tissue specific expression pattern of this MFS transporter is also described in the specification as filed on page 3, line 30. Thus, clearly Appellants have asserted that the sequences of the present invention encode a novel human transporter protein and as described in the specification as filed (on page 16, lines 19-23) was the role of such transporters and transporter related multidrug resistance (MDR) sequences, as well as uses and applications that are germane to the described transporter as described in U.S. Patents Nos. 5,198,344 and 5,866,699 which were incorporated by reference in their entirety. Furthermore, it even appears that the Examiner eventually does recognize this (on page 6, lines 6-8 of the Examiner's Answer) That "Though Appellants have clearly stated that the protein of the present invention is a transporter protein .....Appellants have still not provided any conclusive evidence that the protein of the present invention is a transport protein."

Additional evidence was previously provided to the Examiner, that further demonstrates that those of skill in the art would find the assertion that the sequences of the present invention encode a transporter

protein credible, was a compilation of the results of functional protein domain analyses using several of the available methods known to and accepted by those of skill in the art as Exhibit A of the Appeal Brief. InterPro (http://www.ebi.ac.uk/interpro/) is a publically database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences. InterPro analysis of SEQ ID NO:2 of the present invention clearly shows it to be, as Appellants have asserted, *a transporter protein.* Pfam (http://www.sanger.ac.uk/Software/Pfam/index.shtml) is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains and families. Pfam analysis of SEQ ID NO:2 of the present invention once again clearly shows the present invention to be, as Appellants have asserted, *a transporter protein.* ProtComp analysis (http://www.hgmp.mrc.ac.uk/GenomeWeb/prot-anal.html)is used in identifying sub-cellular location of a protein in animals and fungi. Results of a ProtComp analysis of SEQ ID NO:2 of the present invention shows it to be an integral membrane protein. Appellants have asserted that the sequences of the present invention encode a transporter protein, whose function is to mediate or facilitate the passage of materials across the lipid bilayer, thus logically those of skill in the art would recognize that *transporter proteins are very often integral membrane proteins.* SMART (a Simple Modular Architecture Research Tool: http://smart.embl-heidelberg.de/) analysis allows the identification and annotation of genetically mobile domains and the analysis of domain architectures. More than 500 domain families found in signaling, extracellular and chromatin-associated proteins are detectable. These domains are extensively annotated with respect to phyletic distributions, functional class, tertiary structures and functionally important residues. Each domain found in a non-redundant protein database as well as search parameters and taxonomic information are stored in a relational database system. SMART analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, a *transporter protein.* TMHMM analysis (http://www.cbs.dtu.dk/services/TMHMM/) predicts transmembrane helices in proteins and TMHMM analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be an integral transmembrane protein, as those of skill in the art would expect of a *transporter protein.* Finally, ProDom analysis (http://prodes.toulouse.inra.fr/prodom/2002.1/html/home.php) is a comprehensive set of protein domain families automatically generated from the SWISS-PROT and TrEMBL sequence databases.

ProDom analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, *a transporter protein*. In summary, all of the evidence presented as a result of analysis using a series of different methods recognized by those of skill in the art, clearly agree and identify the sequences of the present invention as encoding an integral membrane transporter protein, as Appellants had asserted in the specification as filed. Therefore, clearly, Appellants' assertion that the sequences of the present invention encode a transporter protein are credible and would be accepted by those of skill in the art.

Finally, the Examiner appears to recognize that transporter proteins have specific and substantial utility (lines 10-12 on page 6 of the Examiner's Answer) and Appellants submit that the legal test for utility is not "conclusive evidence", rather simply an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Therefore, as Appellants have made the credible assertion that the sequences of the present invention encode a MFS transporter protein and transporter proteins are known to have specific and substantial utility and play a role in multiple drug resistance by human tumors, the logical conclusion is that the sequences of present invention also have patentable utility and rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

The Examiner also discounts several arguments concerning the utilities of the sequences of the present invention since other nucleic acid sequences can be used in a similar fashion. In addition to the detailed arguments presented by Appellants in the Appeal Brief with regard to each of these asserted utilities, Appellants once again point out that these arguments are completely rebuffed by the Federal Circuit's holding in *Carl Zeiss, supra* ("[A]n invention need not be the best or only way to accomplish a

certain result"). As the main argument concerning this utility and that of use of the specific sequences on DNA chips (presented below) is that since other nucleic acid sequences can be used to map the human chromosome or on DNA chips, these do not represent specific or substantial utilities. However, as previously presented, don't all golf balls and tires have the same utility of other golf balls or tires, i.e. they can be used as golf balls or tires respectively and yet these items are readily considered to have patentable utility.

Furthermore, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. In fact some such gene chips have contained randomly generated sequence.

However, in contrast the sequences of the present invention provide a specific marker of the gene that is transcribed, spliced and encodes a novel human transporter that is expressed in some human tissues and not others. Thus, these sequences provide a unique identifier of the corresponding gene in the human genome. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the

specification details. The Examiner agrees that such "DNA chips" have utility, as evidenced by hundreds of issued U.S. Patents, but argues that specific sequences which clearly increase the utility of a patented invention do not. It must be noted that this position runs counter to that made by the Examiner regarding golf balls, wherein the presence of a specific feature that enhances the utility of the golf ball has utility.

For each of the foregoing reasons, as well as the reasons set forth in the Appeal Brief, Appellants submit that the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 1-3, 13 and 14 Unusable Due to a Lack of Patentable Utility?

Regarding the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility, Appellants submit that as claims 1-3, 13 and 14 have been shown to have "a specific, substantial, and credible utility", as detailed in Section X(A) above, as well as Section VIII(A) of the Appeal Brief, the present rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-3, 13 and 14 under 35 U.S.C. § 112, first paragraph, must be overruled.

XI. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-3, 13 and 14 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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